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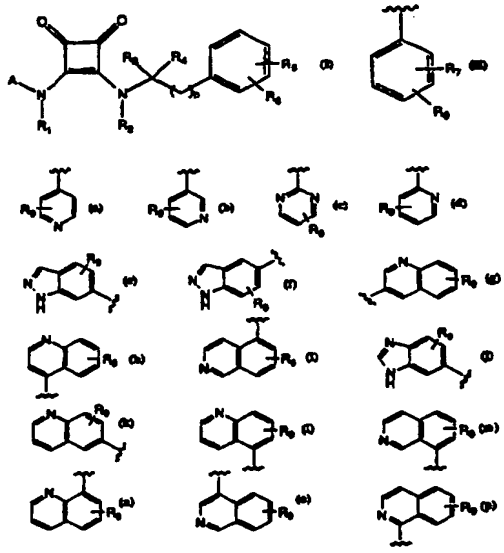
(54) Title: N-ARYL AND N-HETEROARYL-1,2-DIAMINOCYCLOBUTENE-3,4-DIONES WITH SMOOTH MUSCLE RELAXING ACTIVITIES

(57) Abstract

The compounds of formula (I), wherein R_1 is hydrogen, C_{1-10} straight or branched chain alkyl, C_{3-10} cyclic or bicyclic alkyl, alkanoyl of 2 to 7 carbon atoms, alkylsulfonyl of 1 to 7 carbon atoms, aroyl of 7 to 12 carbon atoms, arylalkenoyl of 9 to 20 carbon atoms, arylsulfonyl of 6 to 12 carbon atoms, arylalkanoyl of 8 to 12 carbon atoms or arylalkylsulfonyl of 7 to 12 carbon atoms; R_2 is hydrogen, C_{1-10} straight or branched chain alkyl or C_{3-10} cyclic or bicyclic alkyl; A is a group of formula (II), wherein R_7 and R_8, independent from each other, are selected from the following: cyano, nitro, amino, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, amino, C_{1-12} mono- or dialkylamino, sulfonamide, C_{1-6} alkylsulfonamido, C_{6-12} arylsulfonamido, C_{2-6} alkylcarboxamido, C_{7-12} arylcarboxamido, C_{1-6} alkylsulfonyl, C_{1-6} perfluoroalkylsulfonyl, C_{6-12} arylsulfonyl, chloro, bromo, fluoro, iodo, 1-imidazolyl, carboxyl, carboalkoxy of 2 to 7 carbon atoms, hydroxyl or hydrogen; or A is Het where Het is selected from (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (m), (n), (o), (p), wherein R_9 is hydrogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, amino, C_{1-12} mono- or dialkylamino, C_{1-6} alkylsulfonamido, C_{2-6} alkylcarboxamido, nitro, cyano, carboxyl, chloro, bromo, fluoro, iodo; n is an integer from 0 to 6; R_3 and R_4 are, independent from each other, hydrogen, C_{1-10} straight or branched chain alkyl, or C_{3-10} cyclic or bicyclic alkyl; C_{1-10} perfluoro alkyl, C_{1-10} hydroxyalkyl, C_{2-10} alkoxyalkyl, fluoro; or, when taken together, form a spirocyclic ring containing a total of 3-7 carbon atoms; R_5 and R_6, independent from each other, are selected from the following: cyano, nitro, amino, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, amino, C_{1-12} mono- or dialkylamino, sulfonamide, C_{1-6} alkylsulfonamido, C_{6-12} arylsulfonamido, C_{2-6} alkylcarboxamido, C_{7-12} arylcarboxamido, C_{1-6} alkylsulfonyl, C_{1-6} perfluoroalkylsulfonyl, C_{6-12} arylsulfonyl, chloro, bromo, fluoro, iodo, 1-imidazolyl, carboxyl, C_{2-7} carboalkoxy, hydroxyl, or hydrogen; or a pharmaceutically acceptable salt thereof.



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N-Aryl and N-Heteroaryl-1,2-Diaminocyclobutene-3,4-diones with smooth muscle relaxing activities

Background of Invention

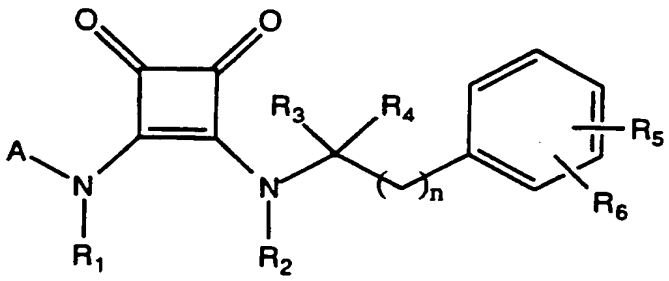
The present invention relates to novel 1, 2-diamino derivatives of cyclobutene 3-4-diones having pharmacological activity, to a process for their preparation, to pharmaceutical compositions containing them, and to their use in the treatment of disorders associated with smooth muscle contraction; via potassium channel modulation. Such disorders include, but are not limited to: urinary incontinence, hypertension, asthma, premature labor, irritable bowel syndrome, congestive heart failure, angina, and cerebral vascular disease.

Stemp et al. disclose a class of amino substituted cyclobutenedione derivatives of chromans described as having blood pressure lowering activity and bronchodilatory activity in EP-426379-A2. Several series of 1-amino-2-phenylalkylamino-cyclobutene-3,4-diones are reported as H-2 receptor antagonists by Algieri et al. in US Patent 4,390,701 and its numerous divisionals and CIPs. Several related 1-amino-2-phenoxyalkylamino derivatives are disclosed by Nohara et al. in US Patent 4,673,747.

The synthesis of representative 1,2-diamino-cyclobutene-3,4-diones are described in the following publications: Tietze et al., *Chem Ber.* 1991, *124*, 1215; Tietze et al., *Bioconjugate Chem.* 1991, 2, 148; Ehrhardt et al., *Chem. Ber.* 1977, *110*, 2506, and Neuse et al., *Liebigs Ann. Chem.* 1973, 619.

Description of The Invention

Accordingly, the present invention discloses compounds represented by the formula (I):



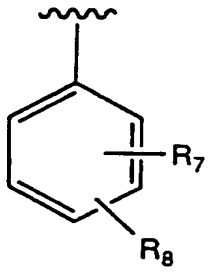
(I)

wherein:

R_1 is hydrogen, C_{1-10} straight or branched chain alkyl, C_{3-10} cyclic or bicyclic alkyl, alkanoyl of 2 to 7 carbon atoms, alkylsulfonyl of 1 to 7 carbon atoms, aroyl of 7 to 12 carbon atoms, arylalkenoyl of 9 to 20 carbon atoms, arylsulfonyl of 6 to 12 carbon atoms, arylalkanoyl of 8 to 12 carbon atoms or arylalkylsulfonyl of 7 to 12 carbon atoms;

R_2 is hydrogen, C_{1-10} straight or branched chain alkyl or C_{3-10} cyclic or bicyclic alkyl;

A is a group of the following formula:

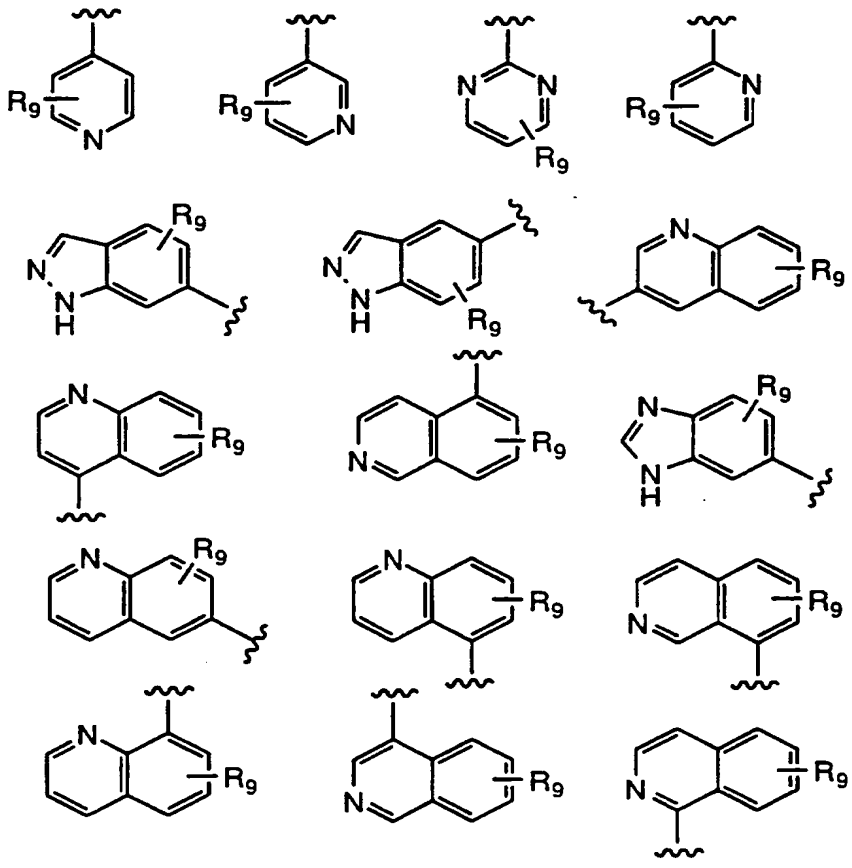


wherein:

R_7 and R_8, independent from each other, are selected from the following: cyano, nitro, amino, C_{1-6} alkyl,

C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, amino, C_{1-12} mono- or dialkylamino, sulfonamide, C_{1-6} alkylsulfonamido, C_{6-12} arylsulfonamido, C_{2-6} alkylcarboxamido, C_{7-12} arylcarboxamido, C_{1-6} alkylsulfonyl, C_{1-6} perfluoroalkylsulfonyl, C_{6-12} arylsulfonyl, chloro, bromo, fluoro, iodo, 1-imidazolyl, carboxyl, carboalkoxy of 2 to 7 carbon atoms, hydroxyl or hydrogen;

or, A is Het where Het is selected from the following:



wherein:

R_9 is hydrogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, amino, C_{1-12} mono- or dialkylamino, C_{1-6} alkylsulfonamido, C_{2-6} alkylcarboxamido, nitro, cyano, carboxyl, chloro, bromo, fluoro, iodo;

n is an integer from 0 to 6;

R_3 and R_4 are, independent from each other, hydrogen, C_{1-10} straight or branched chain alkyl , or C_{3-10} cyclic or bicyclic alkyl; C_{1-10} perfluoro alkyl, C_{1-10} hydroxyalkyl, C_{2-10} alkoxyalkyl, fluoro; or, when taken together, form a spirocyclic ring containing a total of 3-7 carbon atoms;

R_5 and R_6, independent from each other, are selected from the following: cyano, nitro, amino, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, amino, C_{1-12} mono- or dialkylamino, sulfonamide, C_{1-6} alkylsulfonamido, C_{6-12} arylsulfonamido, C_{2-6} alkylcarboxamido, C_{7-12} arylcarboxamido, C_{1-6} alkylsulfonyl, C_{1-6} perfluoroalkylsulfonyl, C_{6-12} arylsulfonyl, chloro, bromo, fluoro, iodo, 1-imidazolyl, carboxyl, C_{2-7} carboalkoxy, hydroxyl, or hydrogen;

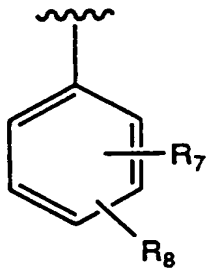
or a pharmaceutically acceptable salt thereof.

A preferred aspect of this invention includes compounds of formula (I)

wherein:

R_1 and R_2 are as stated above;

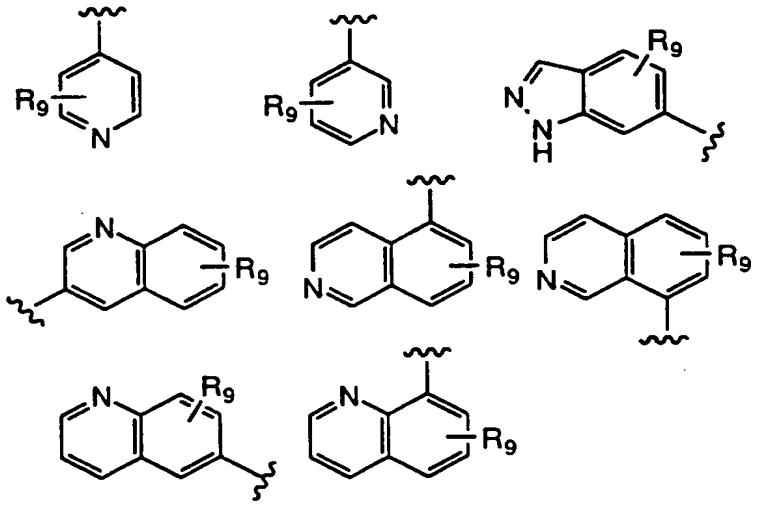
A is a group of the following formula:



wherein:

R7 and R8, independent from each other, are selected from the following: cyano, nitro, amino, chloro, bromo, fluoro, iodo, 1-imidazolyl, carboxyl, hydrogen;

or A is Het where Het is selected from the following:



wherein:

R9 is as stated above;

n = 0;

R_3 and R_4 are, independent from each other, hydrogen, C_{1-10} straight or branched chain alkyl, C_{1-10} perfluoro alkyl, C_{1-10} hydroxyalkyl or fluoro;

R_5 and R_6, independent from each other, are selected from the following: cyano, nitro, amino, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, amino, chloro, bromo, fluoro, iodo, carboxyl, C_{2-7} carboalkoxy, hydroxyl, hydrogen;

or a pharmaceutically acceptable salt thereof.

It is understood that the definition of the compounds of formula (I), when R_1, R_2, R_3, R_4, R_5, or R_6 contain asymmetric carbons, or when R_3 is different from R_4, encompass all possible stereoisomers and mixtures thereof. In particular, it encompasses racemic modifications and optical isomers. The optical isomers may be obtained in pure form by standard separation techniques. The pharmaceutically acceptable salts are those derived from such organic and inorganic acids as: lactic, citric, acetic, tartaric, succinic, maleic, malonic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, and similarly known acceptable acids. Where R_3, R_4, R_5 or R_6 are carboxyl groups, salts of the compounds of this invention may be formed with bases such as alkali metals (Na, K, Li) or the alkaline earth metals (Ca or Mg).

The acyl groups representing R_1 are derived from such acids as acetic, propionic, butyric, valeric, caproic, methanesulfonic, ethanesulfonic, benzoic, toluic, cinnamic, phenylsulfonic, phenylacetic, naphthylacetic, benzylsulfonic and the like.

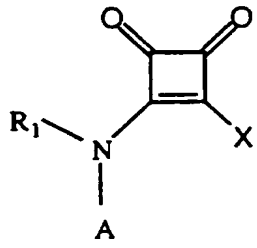
Examples of alkyl as a group or part of a group, e.g. alkoxy, aryl are alkyl groups of 1-4 carbon atoms such as methyl, ethyl, propyl and butyl.

The term aryl when used for a group or part of a group, e.g. arylalkyl, aroyl, includes carbocyclic aromatic groups of 6 to 10 carbon atoms, e.g. phenyl and naphthyl such as 1-naphthyl.

Examples of perfluoroalkyl group are such groups having 1-4 carbon atoms, e.g. perfluoromethyl and perfluoroethyl.

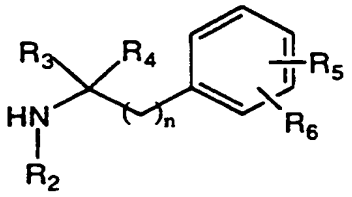
The present invention also provides processes for the preparation of compounds of formula (I). Accordingly, this invention provides a process for preparing a compound of formula I which comprises:

a) reacting a compound of the formula:



(II)

wherein X is a leaving group and A and R_1 are as defined above, with a compound of formula:



(III)

wherein n and R_{2-6} are as defined above to give a compound of formula I; or

b) reacting a compound of formula I wherein R_1 is hydrogen with an alkylating or acylating agent containing R_1 where R_1 is as defined above expecting hydrogen in the presence of a base to give a compound of formula I where R_1 is other than hydrogen; or

c) converting an acidic compound of formula I wherein at least one of R_5-R_9 is a carboxy group to a salt with a base, e.g. alkali metal, alkaline earth metal or optionally substituted ammonium salt; or

d) converting a basic compound of formula I to a pharmaceutically acceptable acid addition salt; or

e) isolating an optically active isomer of a compound of formula I from a mixture of isomers; or

f) reacting a compound of formula I having a reactive site or substituent group to give a different compound of formula I.

Conveniently the compounds of formula I may be prepared by reacting a compound of formula II.

As mentioned previously, the compounds of formula (I) have been found to relax smooth muscle. They are therefore useful in the treatment of disorders associated with smooth muscle contraction, disorders involving excessive smooth muscle contraction of the urinary tract (such as incontinence), or of the gastro-intestinal tract (such as irritable bowel syndrome), asthma, and hair loss. Furthermore, the compounds of formula (I) are active as potassium channel activators which render them useful for treatment of peripheral vascular disease, congestive heart failure, stroke, anxiety, cerebral anoxia and other neurodegenerative disorders.

The present invention accordingly provides a pharmaceutical composition which comprises a compound of this invention and a pharmaceutically acceptable carrier. In particular, the present invention provides a pharmaceutical composition which comprises an effective amount of a compound of this invention and a pharmaceutically acceptable carrier.

The compositions are preferably adapted for oral administration. However, they may be adapted for other modes of administration, for example parenteral administration for patients suffering from heart failure.

In order to obtain consistency of administration, it is preferred that a composition of the invention is in the form of a unit dose. Suitable unit dose forms include tablets, capsules and powders in sachets or vials. Such unit dose forms may contain from 0.1 to 100 mg of a compound of the invention and preferably from 2 to 50 mg. Still further preferred unit dosage forms contain 5 to 25 mg of a compound of the present invention. The compounds of the present invention can be administered orally at a dose range of about 0.01 to 100 mg/kg or preferably at a dose range of 0.1 to 10 mg/kg. Such compositions may be administered from 1 to 6 times a day, more usually from 1 to 4 times a day.

The compositions of the invention may be formulated with conventional excipients, such as a filler, a disintegrating agent, a binder, a lubricant, a flavoring agent and the like. They are formulated in conventional manner, for example, in a manner similar to that used for known antihypertensive agents, diuretics and β-blocking agents.

The present invention further provides a compound of the invention for use as an active therapeutic substance. Compounds of formula (I) are of particular use in inducing smooth muscle relaxation.

The present invention further provides a method of treating smooth muscle disorders in mammals including man, which comprises administering to the afflicted mammal an effective amount of a compound or a pharmaceutical composition of the invention.

The following examples are presented to illustrate rather than limit the methods for production of representative compounds of the invention.

EXAMPLE 1

4-[3,4-Dioxo-2-((R)-1-phenyl-ethylamino)-cyclobut-1-enylamino]-benzonitrile

Step 1) Preparation of 4-(3,4-Dioxo-2-ethoxy-cyclobut-1-enylamino)-benzonitrile

4-Aminobenzonitrile (3.47 g, 29.4 mmol) was added to a solution of 3,4-diethoxy-3-cyclobutene-1, 2-dione (5.00 g, 29.4 mmol) in absolute ethanol (100 mL). The mixture was heated at reflux overnight. The mixture was cooled, and the resulting yellow precipitate was collected by vacuum filtration. Yield: 2.60 g (37%): mp 218-222°C; ^{1}H NMR (DMSO-d_6): δ 11.07 (s, 1H), 7.81 (d, 2H), 7.56 (d, 2H), 4.79 (q, 2H), 1.46 (t, 3H).

Step 2) Preparation of 4-[3,4-dioxo-2-((R)-1-phenyl-ethylamino)-cyclobut-1-enylamino]-benzonitrile

To the above squarate (0.50 g, 2.06 mmol) in ethanol (10 mL) was added (R)-α-methylbenzylamine (0.27 mL, 2.1 mmol). The mixture was heated at reflux for 16 hours and vacuum filtered. The precipitate was recrystallized from methanol to afford 0.17 g (26%) of product as a pale yellow solid: mp 273-274°C ; $[\alpha]^{25}_D$ -53.20 (DMSO); ^{1}H NMR (DMSO-d_6): δ 9.91 (s, 1H), 8.21 (d, 1H), 7.72 (d, 1H), 7.79-7.31 (m, 9H), 5.29 (m, 1H), 1.59 (d, 3H). IR (KBr): 3200, 2230, 1790, 1670, 1600 cm^{-1}; MS (m/z) 317 (M^+).

Elemental analysis for $C_{19}H_{15}N_3O_2$

Calc'd: C, 71.91; H, 4.76; N, 13.24.

Found: C, 71.26; H, 4.86; N, 13.49.

EXAMPLE 2

3-(5-Bromo-pyridin-3-ylamino)-4-((R)-1-phenyl-ethylamino)-cyclobut-3-ene-1,2-dione

Step 1) Preparation of 3-(5-bromo-pyridin-3-ylamino)-4-ethoxy-cyclobut-3-ene-1,2-dione)

3-Amino-5-bromopyridine (1.92 g, 11.3 mmol) was added to a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (2.24 g, 11.1 mmol) in absolute ethanol (30 mL). The mixture was heated at reflux for 18 hours, cooled and filtered. The filtrate was concentrated and the resulting residue chromatographed (CH_3OH/CH_2Cl_2) to

afford 2.06 g (62%) of product as an off-white solid: ^{1}H NMR (DMSO-d_6): δ 11.00 (s, 1H), 8.56 (s, 1H), 8.42 (s, 1H), 8.09 (s, 1H), 4.79 (q, 2H), 1.42 (t, 3H).

Step 2) Preparation of 3-(5-Bromo-pyridin-3-ylamino)-4-((R)-1-phenyl-ethylamino)-cyclobut-3-ene-1,2-dione

To the above squarate (0.815 g, 2.74 mmol) in ethanol (25 mL) was added (R)-α-methylbenzylamine (0.36 mL, 2.8 mmol). The mixture was heated at reflux for 23 hours. The precipitate was filtered off and rinsed with ethanol to afford 0.92 g (90%) of product as an off-white solid: mp 268-271°C (dec); $[\alpha]^{25}_D$ +6.57 (DMSO); ^{1}H NMR (DMSO-d_6): δ 9.85 (s, 1H), 8.44-8.15 (m, 4H), 7.43-7.27 (m, 5H), 5.29 (m, 1H), 1.59 (d, 3H). IR (KBr): 3200, 1790, 1670, 1590 cm^{-1}; MS (m/z) 372 (MH^+).

Elemental analysis for $C_{17}H_{14}BrN_3O_2$

Calc'd: C, 54.86; H, 3.79; N, 11.29.

Found: C, 54.88; H, 3.67; N, 11.20.

EXAMPLE 3

3-(2-Methoxy-5-trifluoromethyl-phenylamino)-4-((R)-1-phenyl-ethylamino)-cyclobut-3-ene-1,2-dione

Step 1) Preparation of 3-ethoxy-4-(2-methoxy-5-trifluoromethyl-phenylamino)-cyclobut-3-ene-1,2-dione

2-Methoxy-5-trifluoromethylaniline (5.62 g, 29.4 mmol) was added to a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (5.00 g, 29.4 mmol) in absolute ethanol (100 mL). The mixture was heated at reflux for 66 hour, cooled and filtered. The precipitate was purified by chromatography (CH_3OH/CH_2Cl_2) to afford 1.88 g (20%) of product as a yellow solid: ^{1}H NMR (DMSO-d_6): δ 10.42 (s, 1H), 7.64-7.20 (m, 3H), 4.69 (q, 2H), 3.90 (s, 3H), 1.34 (t, 3H).

Step 2) Preparation of 3-(2-methoxy-5-trifluoromethyl-phenylamino)-4-((R)-1-phenyl-ethylamine)-cyclobut-3-ene-1,2-dione

To the above squarate (0.806 g, 2.56 mmol) in ethanol (10 mL) was added (R)-α-methylbenzylamine (0.33 mL, 2.6 mmol). The mixture was heated at reflux for 23 hours. The clear yellow solution was concentrated and the resulting foam purified by chromatography (CH_3OH/CH_2Cl_2)to afford 0.84 g (84%) of product as a white solid: mp 115-124°C ; $[\alpha]^{25}_D$ -33.61 (DMSO); ^1H NMR (DMSO-d_6): δ 9.37 (s, 1H), 8.72 (d, 1H), 8.24 (s, 1H), 7.42-7.19 (m, 7H), 5.33 (m, 1H), 3.97 (s, 1H), 1.59 (d, 3H). IR (KBr): 3250, 1790, 1690, 1610 cm^{-1}; MS (m/z) 391 (MH^+).

Elemental analysis for $C_{20}H_{17}F_3N_2O_3$

Calc'd: C, 61.54; H, 4.39; N, 7.18.

Found: C, 61.42; H, 4.26; N, 7.23.

EXAMPLE 4

3-((R)-1-Phenyl-ethylamino)-4-(pyridin-4-ylamino)-cyclobut-3-ene-1,2-dione

Step 1) Preparation of 3-ethoxy-4-(pyridin-4-ylamino)-cyclobut-3-ene-1,2-dione

To a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (5.00 g, 29.4 mmol) in ethanol (100 mL) was added a suspension of 4-aminopyridine (2.77 g, 29.4 mmol) in ethanol (50 mL). The reaction mixture was heated at reflux for 4 hours. Concentration and chromatography (EtOAc) of the resulting residue afforded 0.632 g (10%) of product as a white solid: ^1H NMR (DMSO-d_6): δ 11.18 (br s, 1H), 8.45 (d, 2H), 7.40 (d, 2H), 4.80 (q, 2H), 1.43 (t, 3H).

Step 2) Preparation of 3-((R)-1-phenyl-ethylamino)-4-(pyridin-4-ylamino)-cyclobut-3-ene-1,2-dione

To the above squarate (0.850 g, 3.90 mmol) in ethanol (25 mL) was added (R)-α-methylbenzylamine (0.51 mL, 4.0 mmol). The mixture was heated at reflux for 23 hours. The precipitate was filtered off and rinsed with ethanol. Chromatography (CH_3OH/CH_2Cl_2) afforded 0.276 g (24%) of product as an off-white solid: mp 252-254°C (dec); $[\alpha]^{25}_D$ -31.45 (DMSO); ^1H NMR (DMSO-d_6): δ 9.82 (s, 1H), 8.40 (d,

2H), 8.22 (d, 1H), 7.45-7.38 (m, 7H), 5.28 (m, 1H), 1.59 (d, 3H). IR (KBr): 3200, 1800, 1675, 1590 cm^{-1}; MS (m/z) 293 (MH^+).

Elemental analysis for $C_{17}H_{15}N_3O_2$

Calc'd: C, 69.61; H, 5.15; N, 14.33.

Found: C, 69.49; H, 5.06; N, 14.18.

EXAMPLE 5

4-[3,4-Dioxo-2-((S)-1-phenyl-ethylamino)-cyclobut-1-enylamino]-benzonitrile

To the squarate of Example 1, step 1 (0.50 g, 2.06 mmol) in ethanol (10 mL) was added (S)-α-methylbenzylamine (0.27 mL, 2.1 mmol). The mixture was heated at reflux for 16 hours and vacuum filtered. The precipitate was recrystallized from methanol to afford 0.17 g (26%) of product as a pale yellow solid: mp 269-270°C ; $[\alpha]^{25}_D$ +46.47 (DMSO); ^1H NMR (DMSO-d_6): δ 9.91 (s, 1H), 8.21 (d, 1H), 7.72 (d, 1H), 7.79-7.31 (m, 9H), 5.29 (m, 1H), 1.59 (d, 3H). IR (KBr): 3200, 2230, 1790, 1670, 1600 cm^{-1}; MS (m/z) 317 (M^+).

Elemental analysis for $C_{19}H_{15}N_3O_2$

Calc'd: C, 71.91; H, 4.76; N, 13.24.

Found: C, 71.17; H, 4.83; N, 13.34.

EXAMPLE 6

3-(4-Trifluoromethoxy-phenylamino)-4-((R)(-)-1-phenyl-ethylamino)-cyclobut-3-ene-1,2-dione

Step 1) Preparation of 3-ethoxy-4-(4-trifluoromethoxy-phenylamino)-cyclobut-3-ene-1,2-dione

4-Trifluoromethoxyaniline (5.00 g, 28.2 mmol) was added to a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (5.00 g, 29.4 mmol) in absolute ethanol (50 mL). The mixture was heated at reflux overnight, then vacuum filtered hot. The filtrate was reduced in volume and the resulting precipitate was filtered to afford 4.50

g (53%) of white solid: mp 145-146°C; ^{1}H NMR (DMSO-d_6): δ 10.87 (s, 1H), 7.45 (d, 2H), 7.36 (d, 2H), 4.75 (q, 2H), 1.41 (t, 3H).

Step 2) Preparation of 3-(4-trifluoromethoxy-phenylamino)-4-((R)-1-phenyl-ethylamine)-cyclobut-3-ene-1,2-dione

To the above squarate (0.330 g, 1.10 mmol) in ethanol (25 mL) was added (R)-α-methylbenzylamine (0.135 mg, 1.11 mmol). The reaction was refluxed for 23 hours. Upon cooling, the product precipitated as a white solid 0.350g (84%): mp 258-260°C ; $[\alpha]^{25}_D$ -17.52 (DMSO); ^{1}H NMR (DMSO-d_6): δ 9.70 (s, 1H), 8.12 (d, 1H), 7.51-7.28 (m, 9H), 5.28 (m, 1H), 1.59 (d, 3H). IR (KBr): 3250, 1800, 1675, 1600 cm^{-1}; MS (m/z) 377 (MH^+).

Elemental analysis for $C_{19}H_{15}F_3N_2O_3$

Calc'd: C, 60.64; H, 4.02; N, 7.44.

Found: C, 60.40; H, 4.01; N, 7.21.

EXAMPLE 7

(R)-4-{2-[1-(4-Nitro-phenyl)-ethylamino]-3,4-dioxo-cyclobut-1-enylamino}-benzonitrile

To the squarate of Example 1, step 1 (0.598 g, 2.47 mmol) in ethanol (50 mL) was added (R)-α-methyl-4-nitrobenzylamine hydrochloride (0.50 g, 2.5 mmol) and N,N-diisopropylethylamine (0.43 g, 2.5 mmol). The mixture was heated at reflux for 16 hours. After cooling the precipitate was filtered off to afford 0.70 g (78%) of product as an orange solid: mp 290-295°C ; $[\alpha]^{25}_D$ -100.52 (DMSO); ^{1}H NMR (DMSO-d_6): δ 9.98 (s, 1H), 8.32 (d, 1H), 8.25 (d, 2H), 7.79 (d, 2H), 7.68 (d, 2H), 7.57 (d, 2H), 5.42 (m, 1H), 1.61 (d, 3H). IR (KBr): 3200, 2220, 1790, 1670, 1600 cm^{-1}; MS (m/z) 362 (M^+).

Elemental analysis for $C_{19}H_{14}N_4O_4$

Calc'd: C, 62.98; H, 3.89; N, 15.46.

Found: C, 62.38; H, 3.73; N, 14.95.

EXAMPLE 8

3-[3,4-Dioxo-2-((R)-1-phenyl-ethylamino)-cyclobut-1-enylaminol-benzonitrile

Step 1) Preparation of 3-(3,4-dioxo-2-ethoxy-cyclobut-1-enylamino)-benzonitrile

3-Aminobenzonitrile (2.06 g, 17.4 mmol) was added to a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (2.97 g, 17.5 mmol) in absolute ethanol (50 mL). The mixture was heated at reflux overnight. The mixture was cooled and the resulting yellow precipitate was collected by vacuum filtration. Yield: 3.40 g (81%): ^{1}H NMR (DMSO-d_6): δ 10.95 (s, 1H), 7.75-7.40 (m, 4H), 4.73 (q, 2H), 1.39 (t, 3H).

Step 2) Preparation of 3-[3,4-dioxo-2-((R)-1-phenyl-ethylamino)-cyclobut-1-enylamino]-benzonitrile

To the above squarate (1.00 g, 4.13 mmol) in ethanol (100 mL) was added (R)-α-methylbenzylamine (0.53 mL, 4.1 mmol). The mixture was heated at reflux overnight and vacuum filtered. The precipitate was triturated twice with hot methanol to afford 0.80 g (61%) of product as a pale yellow solid: mp 289-290°C (dec); $[\alpha]^{25}_D$ -13.9 (DMSO); ^{1}H NMR (DMSO-d_6): δ 9.72 (s, 1H), 8.25 (d, 1H), 7.90-7.28 (m, 9H), 5.30 (m, 1H), 1.60 (d, 3H). IR (KBr): 3200, 2220, 1790, 1650, 1600 cm^{-1}; MS (m/z) 317 (M^+).

Elemental analysis for $C_{19}H_{15}N_3O_2$

Calc'd: C, 71.91; H, 4.76; N, 13.24.

Found: C, 71.80; H, 4.61; N, 13.33.

EXAMPLE 9

4-[3,4-Dioxo-2-(1-methyl-1-phenyl-ethylamino)-cyclobut-1-enylaminol-benzonitrile

To the squarate of Example 1, step 1 (0.81 g, 3.3 mmol) in ethanol (30 mL) was added α,α-dimethylbenzylamine (0.45 g, 3.3 mmol). The mixture was heated at reflux for 20 hours. After cooling the precipitate was filtered off and chromatographed (CH_3OH/CH_2Cl_2) to afford 0.41 g (37%) of product as yellow solid: mp >300°C; ^1H NMR (DMSO-d_6): δ 10.08 (s, 1H), 8.38 (s, 1H), 7.79 (d, 2H), 7.61 (d, 2H), 7.48-7.27 (m, 5H), 1.78 (s, 6H). IR (KBr): 3200, 2230, 1790, 1675, 1600 cm^{-1}; MS (m/z) 331 (M^+).

Elemental analysis for $C_{20}H_{17}N_3O_2$.(0.1 CH_3OH).(0.05 CH_2Cl_2)

Calc'd: C, 71.43; H, 5.21; N, 12.40.

Found: C, 71.30; H, 5.33; N, 12.69.

EXAMPLE 10

4-[3,4-Dioxo-2-((R)-1-phenyl-propylamino)-cyclobut-1-enylaminol-benzonitrile

To the squarate of Example 1, step 1 (1.79 g, 7.39 mmol) in ethanol (30 mL) was added (R)-1-phenyl-propylamine (1.00 g, 7.40 mmol). The mixture was heated at reflux for 18 hours, cooled slightly and vacuum filtered to afford 1.76 g (72%) of product as a yellow solid: mp 242-243°C ; $[\alpha]^{25}_D$ -52.73 (DMSO); ^1H NMR (DMSO-d_6): δ 9.84 (s, 1H), 8.12 (br d, 1H), 7.76 (d, 2H), 7.56 (d, 2H), 7.42-7.27 (m, 5H), 5.06 (m, 1H), 1.94 (m, 2H), 0.90 (t, 3H). IR (KBr): 3200, 2220, 1790, 1670, 1600 cm^{-1}; MS (m/z) 331 (M^+).

Elemental analysis for $C_{20}H_{17}N_3O_2$

Calc'd: C, 72.49; H, 5.17; N, 12.68.

Found: C, 72.42; H, 5.01; N, 12.73.

EXAMPLE 11

4-[3,4-Dioxo-2-((S)-1-phenyl-propylamino)-cyclobut-1-enylaminol-benzonitrile

To the squarate of Example 1, step 1 (1.79 g, 7.39 mmol) in ethanol (30 mL) was added (S)-1-phenyl-propylamine (1.00 g, 7.40 mmol). The mixture was heated at reflux for 18 hours, cooled slightly and vacuum filtered to afford 1.61 g (66%) of product as a yellow solid: mp 241-243°C ; $[\alpha]^{25}_D$ +52.33 (DMSO); ^{1}H NMR (DMSO-d_6): δ 9.84 (s, 1H), 8.21 (br d, 1H), 7.76 (d, 2H), 7.56 (d, 2H), 7.42-7.27 (m, 5H), 5.06 (m, 1H), 1.94 (m, 2H), 0.90 (t, 3H). IR (KBr): 3200, 2220, 1790, 1670, 1600 cm^{-1}; MS (m/z) 331 (M^+).

Elemental analysis for $C_{20}H_{17}N_3O_2$

Calc'd: C, 72.49; H, 5.17; N, 12.68.

Found: C, 72.17; H, 5.04; N, 12.80.

EXAMPLE 12

4-[3,4-Dioxo-2-(benzylamino)-cyclobut-1-enylaminol-benzonitrile

To the squarate of Example 1, step 1 (1.00 g, 4.13 mmol) in ethanol (30 mL) was added benzylamine (0.45 mL, 4.1 mmol). The mixture was heated at reflux for 18 hours, cooled slightly and vacuum filtered. The precipitate was triturated with hot methanol to afford 0.78 g (62%) of product as yellow solid: mp 288-290°C (dec); ^{1}H NMR (DMSO-d_6): δ 9.91 (s, 1H), 8.10 (m, 1H), 7.79 (d, 2H), 7.75 (d, 2H), 7.55 (d, 2H), 7.91-7.78 (m, 5H), 4.82 (d, 2H). IR (KBr): 3190, 2220, 1790, 1660, 1575 cm^{-1}; MS (m/z) 303 (M^+).

Elemental analysis for $C_{18}H_{13}N_3O_2$

Calc'd: C, 71.28; H, 4.32; N, 13.85.

Found: C, 71.07; H, 4.16; N, 12.89.

EXAMPLE 13

(R)-4-{2-[1-(4-Methyl-phenyl)-ethylamino]-3,4-dioxo-cyclobut-1-enylamino}-benzonitrile

To the squarate of Example 1, step 1 (1.00 g, 4.13 mmol) in ethanol (30 mL) was added (R)-1-(*p* -tolyl)-ethylamine (0.56 g, 4.1 mmol). The mixture was heated at reflux for 18 hours, cooled slightly and vacuum filtered to afford 1.02 g (75%) of product as a yellow solid: mp >300°C ; $[\alpha]^{25}_D$ -56.01 (DMSO); ^{1}H NMR (DMSO-d_6): δ 9.81 (s, 1H), 8.10 (m, 1H), 7.76 (d, 2H), 7.55 (d, 2H), 7.29 (d, 2H), 7.19 (d, 2H), 5.26 (m, 1H), 1.57 (d, 3H). IR (KBr): 3200, 2220, 1790, 1670, 1600 cm^{-1}; MS (m/z) 331 (M^+).

Elemental analysis for $C_{20}H_{17}N_3O_2$

Calc'd: C, 72.49; H, 5.17; N, 12.68.

Found: C, 72.42; H, 5.07; N, 12.82.

EXAMPLE 14

(R)-4-{2-[1-(4-Methoxy-phenyl)-ethylamino]-3,4-dioxo-cyclobut-1-enylamino}-benzonitrile

To a solution of (1R, 1'R)-N-(1'-phenylethyl)-1-(4"-methoxyphenyl)-ethylamine (1.37 g, 5.36 mmol; prepared as in *J. Med Chem.* 1992, *35*, 2327) and ammonium formate (1.01 g, 16.0 mmol) in methanol (125 mL) was added 10% palladium on activated carbon. The suspension was refluxed for 2 h, filtered through Celite and concentrated. The squarate of Example 1, step 1 (1.00 g, 4.13 mmol) was added to a solution of the resulting residue in ethanol (30 mL). The mixture was heated at reflux for 18 h, cooled slightly and vacuum filtered. The precipitate was chromatographed (CH_3OH/CH_2Cl_2) and recrystallized (CH_3OH/CH_2Cl_2) to afford 0.21 g (15%) of product as a yellow solid: mp >300°C ; $[\alpha]^{25}_D$ -46.95 (DMSO); ^{1}H NMR (DMSO-d_6): δ 9.89 (s, 1H), 8.13 (d, 1H), 7.77 (d, 2H), 7.56 (d, 2H), 7.34 (d, 2H), 6.95 (d, 2H), 5.23 (m, 1H), 3.73 (s, 3H), 1.57 (d, 3H). IR (KBr): 3200, 2200, 1800, 1670, 1575 cm^{-1}; MS (m/z) 347 (M^+).

Elemental analysis for $C_{20}H_{17}N_3O_3.(0.03\ CH_2Cl_2)$
Calc'd: C, 68.75; H, 4.91; N, 12.01.
Found: C, 68.40; H, 4.74; N, 11.89.

EXAMPLE 15

(R)-4-{3,4-Dioxo-2-[1-(4-trifluoromethoxy-phenyl)-ethylamino]-cyclobut-1-enylamino}-benzonitrile

To a solution of (1R, 1'R)-N-(1'-phenylethyl)-1-(4"-trifluoromethoxyphenyl)-ethylamine (1.92 g, 6.21 mmol; prepared as in *J. Med Chem.* 1992, *35*, 2327) and ammonium formate (1.17 g, 18.6 mmol) in methanol (150 mL) was added 10% palladium on activated carbon. The suspension was refluxed for 2 h, filtered through Celite and concentrated. The squarate of Example 1, step 1 (1.00 g, 4.13 mmol) was added to a solution of the resulting residue in ethanol (35 mL). The mixture was heated at reflux for 18 h, cooled slightly and vacuum filtered. The precipitate was combined with a second crop of solid obtained from the cooled filtrate, chromatographed (CH_3OH/CH_2Cl_2) and recrystallized (CH_3OH/CH_2Cl_2) to afford 0.74 g (45%) of product as a white solid: mp 281-284°C (dec); $[\alpha]^{25}_D$ -55.94 (DMSO); ^1H NMR (DMSO-d_6): δ 9.94 (s, 1H), 8.22 (d, 1H), 7.78 (d, 2H), 7.60-7.51 (m, 4H), 7.40 (d, 2H), 5.33 (m, 1H), 1.60 (d, 3H). IR (KBr): 3200, 2200, 1800, 1670, 1560 cm^{-1}; MS (m/z) 401 (M^+).

Elemental analysis for $C_{20}H_{14}F_3N_3O_3$
Calc'd: C, 59.85; H, 3.52; N, 10.47.
Found: C, 59.94; H, 3.38; N, 10.43.

EXAMPLE 16

4-[3,4-Dioxo-2-(2,2,2-trifluoro-1-phenyl-ethylamino)-cyclobut-1-enylamino]-benzonitrile

To a solution of N-2,2,2-trifluoro-1-phenylethyl-N-1'-(phenyl)ethylamine (1.65 g, 6.22 mmol; prepared as in *J. Org. Chem.* 1977, *42*, 2436) and ammonium formate (1.17 g, 18.6 mmol) in methanol (150 mL) was added 10% palladium on

activated carbon. The suspension was refluxed for 4 h, filtered through Celite and concentrated to a volume of approximately 10 mL. The squarate of Example 1, step 1 (1.00 g, 4.13 mmol) and ethanol (20 mL) were added and the mixture was heated at reflux for 18 h, cooled slightly and vacuum filtered to remove a small amount of solid. The filtrate was chromatographed (CH_3OH/CH_2Cl_2) and the resulting yellow solid crystallized from chloroform and ether to afford 0.72 g (47%) of product as a pale yellow solid: mp 206-207°C ; ^1H NMR (DMSO-d_6): δ 9.99 (s, 1H), 8.88 (d, 1H), 7.82 (d, 2H), 7.60-7.46 (m, 9H), 5.98 (m, 1H), 3.73 (s, 3H). IR (KBr): 3200, 2200, 1800, 1690, 1570 cm^{-1}; MS (m/z) 371 (M^+).

Elemental analysis for $C_{19}H_{12}F_3N_3O_2$

Calc'd: C, 61.46; H, 3.26; N, 11.32.

Found: C, 61.26; H, 3.16; N, 11.23.

EXAMPLE 17

(R)-4-[3,4-Dioxo-2-(1-phenyl-ethylamino)-cyclobut-1-enylaminol-3-methyl-benzonitrile

Step 1) Preparation of 4-(3,4-Dioxo-2-ethoxy-cyclobut-1-enylamino)-3-methylbenzonitrile

4-Amino-3-methylbenzonitrile (1.94 g, 14.7 mmol) was added to a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (2.53 g, 14.9 mmol) in acetonitrile (5 mL). After refluxing the mixture for 24 h a second portion of 3,4-diethoxy-3-cyclobutene-1,2-dione (1.15 g, 6.76 mmol) was added and heating was continued for an additional 48 h. The reaction mixture was diluted with ethyl acetate (50 mL), stirred vigorously and filtered free of undissolved solid. The filtrate was chromatographed (CH_3OH/CH_2Cl_2) to afford 0.90 g (24%) of product as a yellow solid: ^1H NMR (DMSO-d_6): δ 10.50 (s, 1H), 7.76-7.63 (m, 2H), 7.31 (d, 1H), 4.71 (q, 2H), 2.33 (s, 3H), 1.38 (t, 3H).

Step 2) Preparation of (R)-4-[3,4-Dioxo-2-(1-phenyl-ethylamino)-cyclobut-1-enylamino]-3-methyl-benzonitrile

To the above squarate (0.90 g, 3.51 mmol) in ethanol (40 mL) was added (R)-α-methylbenzylamine (0.45 mL, 3.49 mmol). The mixture was heated at reflux for 18 h. The resulting clear solution solution was concentrated and the residue chromatographed (CH_3OH/CH_2Cl_2) to afford 0.98 g (85%) of product as a yellow solid: mp 110-130°C (dec); $[\alpha]^{25}_D$ -40.91 (DMSO); ^1H NMR (DMSO-d_6): δ 8.95 (s, 1H), 8.58 (d, 2H), 7.70-7.28 (m, 8H), 5.36 (m, 1H), 2.33 (s, 3H), 1.61 (d, 3H). IR (KBr): 3250, 2220, 1790, 1690, 1590 cm^{-1}; MS (m/z) 332 (MH^+).

Elemental analysis for $C_{20}H_{17}N_3O_2.(0.10\ CH_2Cl_2)$

Calc'd: C, 71.03; H, 5.10; N, 12.36.

Found: C, 71.37; H, 5.09; N, 12.61.

EXAMPLE 18

(R)-4-[3,4-Dioxo-2-(1-phenyl-ethylamino)-cyclobut-1-enylamino]-3-ethyl-benzonitrile

Step 1) Preparation of 4-(3,4-Dioxo-2-ethoxy-cyclobut-1-enylamino)-3-ethyl-benzonitrile

4-Amino-3-ethylbenzonitrile (2.00 g, 13.7 mmol) was added to a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (2.30 g, 13.5 mmol) in acetonitrile (5 mL). After refluxing the mixture for 24 h a second portion of 3,4-diethoxy-3-cyclobutene-1,2-dione (1.15 g, 6.76 mmol) was added and heating was continued for an additional 24 h. The reaction mixture was diluted with ethyl acetate (45 mL), stirred vigorously and filtered free of undissolved solid. The filtrate was concentrated and the resulting residue was purified by chromatographed (CH_3OH/CH_2Cl_2) and trituration with ether to afford 0.86 g (24%) of product as a light yellow solid: ^1H NMR (DMSO-d_6): δ 10.57 (s, 1H), 7.77-7.66 (m, 2H), 7.31 (d, 1H), 4.71 (q, 2H), 2.73 (q, 2H), 1.37 (t, 3H), 1.13 (t, 3H).

Step 2) Preparation of (R)-4-[3,4-Dioxo-2-(1-phenyl-ethylamino)-cyclobut-1-enylamino]-3-ethyl-benzonitrile

To the above squarate (0.85 g, 3.14 mmol) in ethanol (25 mL) was added (R)-α-methylbenzylamine (0.41 mL, 3.18 mmol). The mixture was heated at reflux for 18 h, cooled slightly and suction filtered. The filtrate was cooled by gradual evaporation of solvent and the precipitate which formed was collected in two crops to afford 0.76 g (70%) of product as an off-white solid: mp 206-207°C (dec); $[\alpha]^{25}_D$ -45.25 (DMSO); ^{1}H NMR (DMSO-d_6): δ 9.98 (s, 1H), 8.55 (d, 2H), 7.68-7.29 (m, 8H), 5.37 (m, 1H), 2.69 (q, 2H), 1.61 (d, 3H), 1.20 (t, 3H). IR (KBr): 3200, 2200, 1800, 1670, 1570 cm^{-1}; MS (m/z) 345 (M^+).

Elemental analysis for $C_{21}H_{19}N_3O_2$

Calc'd: C, 73.03; H, 5.54; N, 12.17.

Found: C, 72.69; H, 5.52; N, 12.18.

EXAMPLE 19

(R)-N-(4-Cyano-phenyl)-N-[3,4-dioxo-2-(1-phenyl-ethylamino)-cyclobut-1-enyl]-acetamide

To a stirred solution of the squarate of Example 1, step 2 (1.77 g, 5.58 mmol) in N,N-dimethylformamide (50 mL) was added, in one portion, sodium hydride (as a 60% dispersion in mineral oil; 0.252 g, 6.30 mmol). The frothy suspension was stirred at rt for 15 min and then at 0°C for an additional 1 h. Acetic anhydride (0.58 mL, 6.15 mmol) was added and the reaction mixture was stirred at 0°C for 1.5 h and then allowed to warm to rt. After an additional 1 h of stirring the reaction solution was concentrated. The resulting yellow solid was washed with successive portions of acetone, methylene chloride and ethyl acetate. The combined washings were concentrated and the resulting residue chromatographed to afford 0.48 g (24%) of product as an off-white solid: mp 240-243°C ; $[\alpha]^{25}_D$ -94.66 (DMSO); ^{1}H NMR (DMSO-d_6): δ 8.29 (d, 1H), 7.96 (d, 2H), 7.69 (d, 2H), 7.45-7.25 (m, 5H), 5.49 (m, 1H), 2.06 (s, 3H), 1.59 (d, 3H). IR (KBr): 3340, 2230, 1800, 1740, 1690, 1610 cm^{-1}; MS (m/z) 359 (M^+).

Elemental analysis for $C_{21}H_{17}N_3O_3.(0.05\ CH_2Cl_2)$

Calc'd: C, 69.53; H, 4.74; N, 11.56.

Found: C, 69.16; H, 4.74; N, 11.53.

Smooth muscle relaxing activity of the compounds of this invention was established in accordance with standard pharmaceutically accepted test procedures in representative compounds as follows:

Sprague-Dawley rats (150-200 g) are rendered unconscious by CO_2 asphyxiation and then euthanized by cervical dislocation. The bladder is removed into warm (37 deg.C) physiological salt solution (PSS) of the following composition (mM): NaCl, 118.4; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4$, 4.7; H_2O, 1.2; $NaHCO_3$, 24.9; KH_2PO_4, 1.2; glucose, 11.1; EDTA, 0.023; gassed with 95% O_2; 2/5% CO_2; pH 7.4. The bladder is opened and then cut into strips 1-2 mm in width and 7-10 mm in length. The strips are subsequently suspended in a 10 mL tissue bath under an initial resting tension of 1.5 g. The strips are held in place by two surgical clips one of which is attached to fixed hook while the other is attached to an isometric force transducer. The preparations, which usually exhibit small spontaneous contractions, are allowed to recover for a period of 1 hour prior to a challenge with 0.1 uM carbachol. The carbachol is then washed out and the tissue allowed to relax to its resting level of activity. Following 1 further 30 min period of recovery an additional 15 mM KCl are introduced into the tissue bath. This increase in KCl concentration results in a large increase in the amplitude of spontaneous contractions (and initiation of contractions in previously quiescent strips) superimposed upon a small increase in basal tone. Following stabilization of this enhanced level of contractile activity, incremental increases in the concentration of test compound or vehicle are introduced into the tissue bath. Contractile activity is measured for each compound or vehicle concentration during the last min of a 30 min challenge.

Isometric force developed by the bladder strips is measured using a concentration required to elicit 50% inhibition of pre-drug contractile activity (IC_{50} concentration) is calculated from this concentration-response curve. The maximum percentage inhibition of contractile activity evoked by a test compound is also recorded for concentrations of test compound < or equal to 30 μM.

The results of this study are shown in Table I.

Table I

Inhibition of Contractions in Isolated Rat Bladder Strips

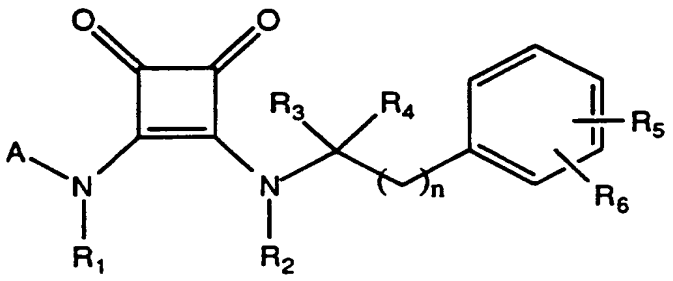
Compound	n	IC_{50}	Inhibition of Force (%) at (x) μM
Example 1	6	0.056 μM	-
Example 4	3	2.3 μM	
Example 5	3	-	38% (30 μM)
Example 9	4	-	22% (30μM)
Example 11	4	-	28% (30μM)

Hence, the compounds of this invention have a pronounced effect on smooth muscle contractility and are useful in the treatment of urinary incontinence, irritable bladder and bowel disease, asthma, hypertension, stroke, and similar diseases as mentioned above, which are amenable to treatment with potassium channel activating compounds by administration, orally, parenterally, or by aspiration to a patient in need thereof.

What is claimed is:

-1-

A compound of the formula:



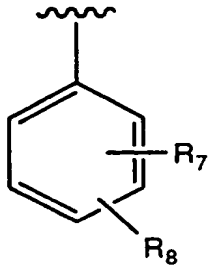
(I)

wherein:

R_1 is hydrogen, C_{1-10} straight or branched chain alkyl, C_{3-10} cyclic or bicyclic alkyl, alkanoyl of 2 to 7 carbon atoms, alkylsulfonyl of 1 to 7 carbon atoms, aroyl of 7 to 12 carbon atoms, arylalkenoyl of 9 to 20 carbon atoms, arylsulfonyl of 6 to 12 carbon atoms, arylalkanoyl of 8 to 12 carbon atoms or arylalkylsulfonyl of 7 to 12 carbon atoms;

R_2 is hydrogen, C_{1-10} straight or branched chain alkyl or C_{3-10} cyclic or bicyclic alkyl;

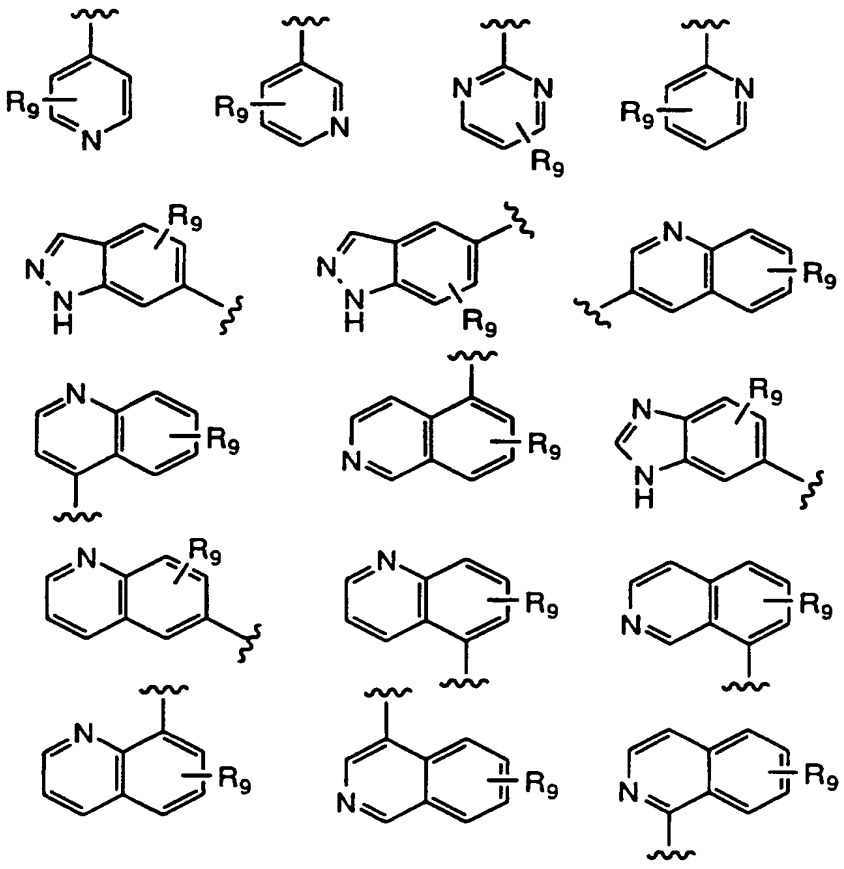
A is a group of the following formula:



wherein:

R7 and R8, independent from each other, are selected from the following: cyano, nitro, amino, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, amino, C_{1-12} mono- or dialkylamino, sulfonamide, C_{1-6} alkylsulfonamido, C_{6-12} arylsulfonamido, C_{2-6} alkylcarboxamido, C_{7-12} arylcarboxamido, C_{1-6} alkylsulfonyl, C_{1-6} perfluoroalkylsulfonyl, C_{6-12} arylsulfonyl, chloro, bromo, fluoro, iodo, 1-imidazolyl, carboxyl, carboalkoxy of 2 to 7 carbon atoms, hydroxyl or hydrogen;

or, A is Het where Het is selected from the following:



wherein:

R9 is hydrogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, amino, C_{1-12} mono- or dialkylamino, C_{1-6} alkylsulfonamido, C_{2-6} alkylcarboxamido, nitro, cyano, carboxyl, chloro, bromo, fluoro, iodo;

n is an integer from 0 to 6;

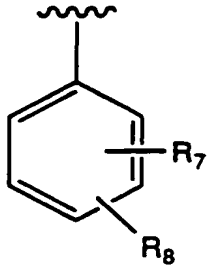
R_3 and R_4 are, independent from each other, hydrogen, C_{1-10} straight or branched chain alkyl , or C_{3-10} cyclic or bicyclic alkyl; C_{1-10} perfluoro alkyl, C_{1-10} hydroxyalkyl, C_{2-10} alkoxyalkyl, fluoro; or, when taken together, form a spirocyclic ring containing a total of 3-7 carbon atoms;

R_5 and R_6, independent from each other, are selected from the following: cyano, nitro, amino, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, amino, C_{1-12} mono- or dialkylamino, sulfonamide, C_{1-6} alkylsulfonamido, C_{6-12} arylsulfonamido, C_{2-6} alkylcarboxamido, C_{7-12} arylcarboxamido, C_{1-6} alkylsulfonyl, C_{1-6} perfluoroalkylsulfonyl, C_{6-12} arylsulfonyl, chloro, bromo, fluoro, iodo, 1-imidazolyl, carboxyl, C_{2-7} carboalkoxy, hydroxyl, or hydrogen;

or a pharmaceutically acceptable salt thereof.

(2) A compound of Claim 1 wherein:

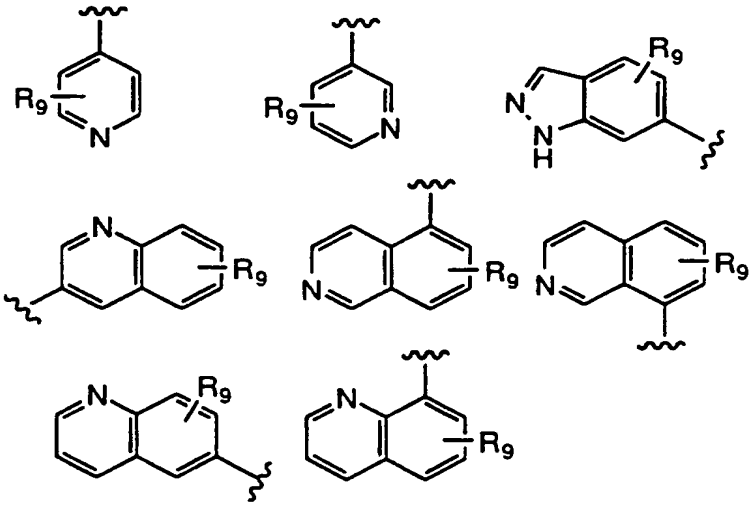
A is a group of the following formula:



wherein:

R7 and R8, independent from each other, are selected from the following: cyano, nitro, amino, chloro, bromo, fluoro, iodo, 1-imidazolyl, carboxyl, hydrogen;

or A is Het where Het is selected from the following:



wherein:

R9 is as stated above;

n = 0;

R_3 and R_4 are, independent from each other, hydrogen, C_{1-10} straight or branched chain alkyl, C_{1-10} perfluoro alkyl, C_{1-10} hydroxyalkyl or fluoro;

R_5 and R_6, independent from each other, are selected from the following: cyano, nitro, amino, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, amino, chloro, bromo, fluoro, iodo, carboxyl, C_{2-7} carboalkoxy, hydroxyl, hydrogen;

or a pharmaceutically acceptable salt thereof.

(3) The compound of Claim 1 which is 4-[3,4-dioxo-2-(1-phenyl-ethylamino)-cyclobut-1-enylamino]-benzonitrile.

(4) The compound of Claim 1 which is 3-(5-bromo-pyridin-3-ylamino)-4-(1-phenyl-ethylamino)-cyclobut-3-ene-1,2-dione.

(5) The compound of Claim 1 which is 3-(2-methoxy-5-trifluoromethyl-phenylamino)-4-(1-phenyl-ethylamino)-cyclobut-3-ene-1,2-dione.

(6) The compound of Claim 1 which is 3-(1-phenyl-ethylamino)-4-(pyridin-4-ylamino)-cyclobut-3-ene-1,2-dione.

(7) The compound of Claim 1 which is 3-(4-trifluoromethoxy-phenylamino)-4-(1-phenyl-ethylamino)-cyclobut-3-ene-1,2-dione.

(8) The compound of Claim 1 which is 4-{2-[1-(4-nitro-phenyl)-ethylamino]-3,4-dioxo-cyclobut-1-enylamino}-benzonitrile.

(9) The compound of Claim 1 which is 3-[3,4-dioxo-2-(1-phenyl-ethylamino)-cyclobut-1-enylamino]-benzonitrile.

(10) The compound of Claim 1 which is 4-[3,4-dioxo-2-(1-methyl-1-phenyl-ethylamino)-cyclobut-1-enylamino]-benzonitrile.

(11) The compound of Claim 1 which is 4-[3,4-dioxo-2-(1-phenyl-propylamino)-cyclobut-1-enylamino]-benzonitrile.

(12) The compound of Claim 1 which is 4-[3,4-dioxo-2-(benzylamino)-cyclobut-1-enylamino]-benzonitrile.

(13) The compound of Claim 1 which is 4-{2-[1-(4-methyl-phenyl)-ethylamino]-3,4-dioxo-cyclobut-1-enylamino}-benzonitrile.

(14) The compound of Claim 1 which is 4-{2-[1-(4-methoxy-phenyl)-ethylamino]-3,4-dioxo-cyclobut-1-enylamino}-benzonitrile.

(15) The compound of Claim 1 which is 4-{3,4-dioxo-2-[1-(4-trifluoromethoxy-phenyl)-ethylamino]-cyclobut-1-enylamino}-benzonitrile.

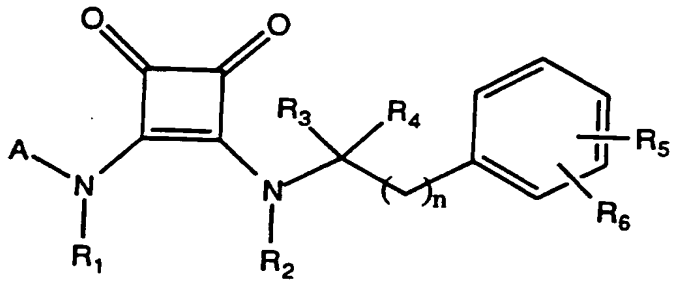
(16) The compound of Claim 1 which is 4-[3,4-dioxo-2-(2,2,2-trifluoro-1-phenyl-ethylamino)-cyclobut-1-enylamino]-benzonitrile.

(17) The compound of Claim 1 which is 4-[3,4-dioxo-2-(1-phenyl-ethylamino)-cyclobut-1-enylamino]-3-methyl-benzonitrile.

(18) The compound of Claim 1 which is 4-[3,4-dioxo-2-(1-phenyl-ethylamino)-cyclobut-1-enylamino]-3-ethyl-benzonitrile.

(19) The compound of Claim 1 which is N-(4-cyano-phenyl)-N-[3,4-dioxo-2-(1-phenyl-ethylamino)-cyclobut-1-enyl]-acetamide.

(20) A method for reducing the adverse effects of smooth muscle contractions which comprises administering, orally or parenterally, to a patient in need thereof, a compound of the formula:



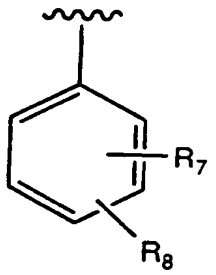
(I)

wherein:

R_1 is hydrogen, C_{1-10} straight or branched chain alkyl, C_{3-10} cyclic or bicyclic alkyl, alkanoyl of 2 to 7 carbon atoms, alkylsulfonyl of 1 to 7 carbon atoms, aroyl of 7 to 12 carbon atoms, arylalkenoyl of 9 to 20 carbon atoms, arylsulfonyl of 6 to 12 carbon atoms, arylalkanoyl of 8 to 12 carbon atoms or arylalkylsulfonyl of 7 to 12 carbon atoms;

R_2 is hydrogen, C_{1-10} straight or branched chain alkyl or C_{3-10} cyclic or bicyclic alkyl;

A is a group of the following formula:

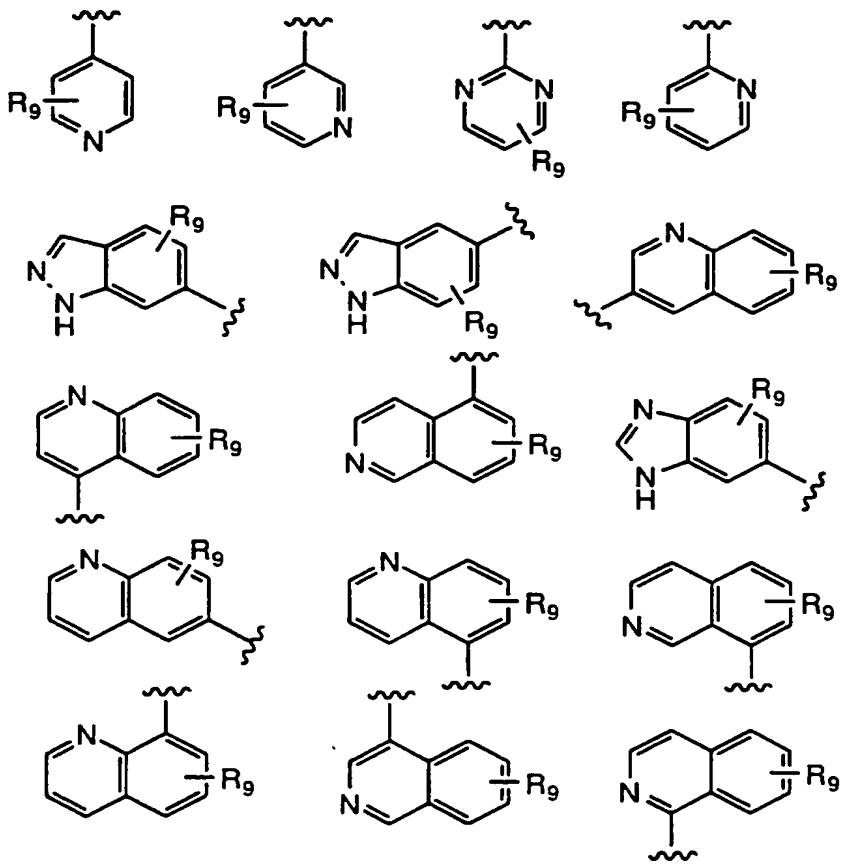


wherein:

R_7 and R_8, independent from each other, are selected from the following: cyano, nitro, amino, C_{1-6} alkyl,

C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, amino, C_{1-12} mono- or dialkylamino, sulfonamide, C_{1-6} alkylsulfonamido, C_{6-12} arylsulfonamido, C_{2-6} alkylcarboxamido, C_{7-12} arylcarboxamido, C_{1-6} alkylsulfonyl, C_{1-6} perfluoroalkylsulfonyl, C_{6-12} arylsulfonyl, chloro, bromo, fluoro, iodo, 1-imidazolyl, carboxyl, carboalkoxy of 2 to 7 carbon atoms, hydroxyl or hydrogen;

or, A is Het where Het is selected from the following:



wherein:

R9 is hydrogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, amino, C_{1-12} mono- or dialkylamino, C_{1-6} alkylsulfonamido, C_{2-6} alkylcarboxamido, nitro, cyano, carboxyl, chloro, bromo, fluoro, iodo;

n is an integer from 0 to 6;

R3 and R4 are, independent from each other, hydrogen, C_{1-10} straight or branched chain alkyl , or C_{3-10} cyclic or bicyclic alkyl; C_{1-10} perfluoro alkyl, C_{1-10} hydroxyalkyl, C_{2-10} alkoxyalkyl, fluoro; or, when taken together, form a spirocyclic ring containing a total of 3-7 carbon atoms;

R5 and R6, independent from each other, are selected from the following: cyano, nitro, amino, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, amino, C_{1-12} mono- or dialkylamino, sulfonamide, C_{1-6} alkylsulfonamido, C_{6-12} arylsulfonamido, C_{2-6} alkylcarboxamido, C_{7-12} arylcarboxamido, C_{1-6} alkylsulfonyl, C_{1-6} perfluoroalkylsulfonyl, C_{6-12} arylsulfonyl, chloro, bromo, fluoro, iodo, 1-imidazolyl, carboxyl, C_{2-7} carboalkoxy, hydroxyl, or hydrogen;

or a pharmaceutically acceptable salt thereof.

(21) The method of Claim 20 in which the smooth muscle adversely contracting causes urinary incontinence.

(22) The method of Claim 20 in which the smooth muscle adversely contracting causes irritable bowel syndrome.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/14597

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/84 C07C49/15 C07C225/20 A61K31/12 A61K31/44
C07D211/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,5 354 763 (BUTERA JOHN A ET AL) 11 October 1994 see the whole document	1-19
P,X	& WO,A,95 14005 (AMERICAN HOME PRODUCTS CORPORATION) 26 May 1995 see the whole document	1-19

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 March 1996	17.04.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Stellmach, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 121, no. 11, 12 September 1994 Columbus, Ohio, US; abstract no. 133584g, SHUICHI,T. ET AL. 'Preparation of 1,2-diaminocyclobutene-3,4-diones and their pharmaceutical use' page 979; see abstract	1-19
X	& JP,A,06 092 915 (SUM ITOMO METAL IND) 5 April 1994 see the whole document	1-19
Y	EP,A,0 426 379 (BEECHAM GROUP PLC) 8 May 1991 cited in the application see the whole document	1-19
Y	EP,A,0 163 324 (IKEDA MOHANDO CO) 4 December 1985 cited in the application see the whole document	1-19
Y	US,A,4 390 701 (ALGIERI ALDO A ET AL) 28 June 1983 cited in the application see the whole document	1-19
Y	EP,A,0 496 561 (AMERICAN HOME PROD) 29 July 1992 see the whole document	1-19
Y	J.MED.CHEM., vol. 35, no. 25, 1992 WASHINGTON, pages 4720-4726, KINNEY,W.A. ET AL. 'Bioisosteric Replacement of the alpha-Amino Carboxylic Acid Functionality in 2-Amino-5-phosphopentanoic Acid Yields Unique 3,4-Diamino-3-cyclobutene-1,2-dione Containing NMDA Antagonists' see the whole document	1-19
Y	TRENDS IN PHARMACOLOGICAL SCIENCE, vol. 11, no. 10, October 1990 CAMBRIDGE, pages 417-422, EDWARDS,G. ET AL. 'Structure-Activity-Relationships of K+ Channel Openers ' * see in particular page 420, * Re-discovered K+ channel openers* *	1-19

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/14597

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO,A,94 29277 (SMITHKLINE BEECHAM PLC ;COATES WILLIAM JOHN (GB); RAWLINGS DEREK A) 22 December 1994 see the whole document ---	1-19
P,Y	EP,A,0 645 385 (SQUIBB BRISTOL MYERS CO) 29 March 1995 see the whole document -----	1-19

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/14597

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 20-22 are directed to a method of treatment of the human/ animal body (Rule 39.1(iv)), the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 95/14597

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-5354763	11-10-94	AU-B-	1086695	06-06-95
		WO-A-	9514005	26-05-95
		US-A-	5401753	28-03-95
		US-A-	5403853	04-04-95
		US-A-	5403854	04-04-95
		US-A-	5397790	14-03-95
EP-A-0426379	08-05-91	AT-T-	115954	15-01-95
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		DE-T-	69015322	18-05-95
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		GB-A,B	2147899	22-05-85
		JP-C-	1625987	18-11-91
		JP-B-	2051425	07-11-90

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 95/14597

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		JP-A-	2036159	06-02-90
		JP-B-	4078628	11-12-92
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		AT-T-	119873	15-04-95
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		AU-B-	1030192	30-07-92
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		DE-D-	69201655	20-04-95
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		CA-A-	2130078	17-03-95
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 95/14597

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0645385		CZ-A-	9402248	16-08-95
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		HU-A-	70614	30-10-95
		JP-A-	7196648	01-08-95
		NO-A-	943428	17-03-95
		PL-A-	305047	20-03-95